REMARKS

Claims 1-12 presently appear in this case. Claims 9 and 11 have been withdrawn from consideration (although they have been made subject to an obviousness rejection). No claims have been allowed. The official action of December 29, 2005, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method for inhibiting aggregation of β-amyloid in a subject or disaggregating aggregated β-amyloid in a subject. To do this, an effective amount of a filamentous bacteriophage that displays an epitope of β-amyloid is administered so as to elicit antibodies against that epitope in the subject. The antibodies that are displayed must be ones that inhibit aggregation of β-amyloid and/or cause disaggregation of β-amyloid. Preferably, the phage is administered intranasally to facilitate passage through the blood-brain barrier.

As to the election of species requirement, because claim 8 has not yet been found to be allowable, the examiner states that it is non-linking and therefore claims 9 and 11 have been withdrawn from further consideration. Applicants understand that upon allowance of a linking or generic claim that all the claims will be examined in this case. Nevertheless, in view of the rejection of claims 9 and 11,

inter alia, under 35 U.S.C. §103, it is apparent that all of the claims can be examined without undue burden on the examiner. Reconsideration and withdrawal of the requirement are therefore respectfully urged.

The examiner has acknowledged applicants' claim for domestic priority under 35 U.S.C. §119(e). However, the examiner states that the priority application fails to provide adequate support for the limitations of claims 5 and 7. The examiner states that claim 11 depends from claim 9 and, thus, also lacks specific support from the provisional. It is not understood from the examiner's comments, however, what effective filing date the examiner is giving to claim 9. The examiner states that the effective filing date for the limitations recited in these claims is the filing date of July 15, 2003.

In view of the fact that the examiner has not cited any intervening references against the claims that she does not consider to be supported in the provisional, it is not necessary to explain at this time why these claims are supported by the disclosure of the provisional application. If and when such an intervening reference is cited against any of such claims, then applicants explicitly reserve the right to explain, in response thereto, why any of such claims are entitled to the effective filing date of the provisional.

Regardless of whether or not the claims in question are supported by the provisional application, the examiner is incorrect that the effective filing date for the limitations recited in these claims is the filing date of July 15, 2003. The present application is a continuation of application 09/473,653, filed December 29, 1999. The present specification is substantially the same as the specification of that application filed in 1999. Accordingly, regardless of whether or not the claims are entitled to the effective filing date of the provisional application, all of the claims are certainly entitled to the effective filing date of parent application 09/473,653, filed December 29, 1999. Acknowledgement of this fact is respectfully urged.

The examiner states that the specification and figures fail to comply fully with the sequence rules as Figure 25 appears to reference amino acid sequences that are not referred to by their appropriate SEQ ID NO either within the figure or within the Brief Description of the Drawings. Appropriate correction has been required.

The description of Figure 25 in the Brief Description of the Drawings has now been amended to refer to the appropriate SEQ ID NOs, which are already present in the sequence listing. Accordingly, no revision of the sequence

listing is necessary, and the amendment to the specification should obviate this objection.

Claims 1-8, 10 and 12 have been provisionally rejected under the judicially creating doctrine of obviousness-type double patenting as being unpatentable over claims 1-20, especially claims 11-13 and 17-20, of co-pending application no. 11/073,526. The examiner states that, while the claims are not identical, the '526 claims stipulate a species of the instant invention, thereby fairly anticipating instant generic claims. The examiner states that both applications teach inhibiting aggregation or removal of amyloid. The examiner states that the patenting of the co-pending claims would render obvious the instant application directed to the generic mechanism of action or function of the Alzheimer's treatment. The examiner states that this is a provisional obviousness-type double patenting rejection because the conflicting claims have not, in fact, been patented.

In view of the fact that this is only a provisional rejection, it is requested that it be held in abeyance until claims of either the present application or application 11/073,526 have been allowed. At that time, a determination can be made as to whether the double patenting rejection is

still applicable and, if so, a terminal disclaimer will be filed.

Claims 1-8, 10 and 12 have been rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. patent 6,919,075. The examiner notes that a timely filed terminal disclaimer may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting patent or application is shown to be commonly owned with this application.

Attached hereto is a terminal disclaimer with respect to U.S. patent 6,919,075. The filing of this terminal disclaimer obviates the present rejection.

Claims 1, 8 and 12 have been rejected under 35 U.S.C. §102(a) as being anticipated by Schenk WO 99/27944 and Schenk U.S. patent 6,787,139. The examiner noted that the two patents are cumulative but that the U.S. patent has an earlier date as a reference, the citations in the rejection being to the PCT publication. The examiner states that Schenk teaches administration of β-amyloid immunogens to a patient in order to generate antibodies to prevent formation of amyloid plaques or to dissolve existing plaques. The examiner states that Schenk also teaches that the agent administered may be displayed via nucleic acid production for presentation within

the host and expressed upon the surface of a virus or bacteria specifically via bacteriophage display methods, citing page 3, line 28, pages 16 and 17, lines 10 and 11. Thus, the examiner considers that the reference's teachings anticipate claims 1, 8 and 12. This rejection is respectfully traversed.

While it is true that Schenk discloses at page 16, lines 14-19, that the agent may be administered displayed on the surface of a virus or bacteria, it discloses nothing whatsoever about the administration of bacteriophage displaying the antigen in question. Schenk nowhere suggests use of a bacteriophage as a delivery vehicle. The viruses suggested are adenovirus, HSV, vaccinia and fowl pox, particularly a fusion to HBsAg. No mention is made of administration by means of display on bacteriophage.

The mention of random libraries of peptides at the paragraph bridging pages 16 and 17 of Schenk does not suggest that such libraries, or any bacteriophage clone selected by means of such libraries, can be directly administered. Of course, it is well known that peptide libraries, can be generated by phage display methods, as is disclosed, for example, by Devlin, but this does not mean that those libraries, or any members of those libraries, can be administered for therapeutic use. Page 17, lines 18-20, indicates that it is the compounds identified by such screens

that are then further analyzed. When speaking of phage-display peptide libraries, it is the peptide that has been selected. The phage is only used in order to present a library. Once the phage-displayed peptide is found to be positive, that peptide is identified, and the peptide itself is then tested further for possible therapeutic use, not the entire bacteriophage displaying that peptide.

Accordingly, as Schenk nowhere discloses the therapeutic administration of a bacteriophage displaying a foreign antigen, none of the present claims are anticipated by Schenk. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 1-12 have been rejected under 35 U.S.C. §103(a) as being unpatentable over either of the two cumulative Schenk references, each alternatively in view of Devlin, Willis, Solomon and Bhardwaj. The examiner recognizes that Schenk does not teach selection of bacteriophage species fd or M13, as is disclosed in claims 2 and 3. The examiner states that Devlin teaches selection of filamentous bacteriophage fd and M13 for preferred production and presentation of peptide antigen. The examiner states that Bhardwaj teaches that the filamentous phages are single-stranded DNA phages that infect male specific *E. coli* strains. The examiner recognizes that Schenk does not teach the

limitation of claims 6, 10 and 11 where the epitopes of β-amyloid are displayed via coat glycoprotein VIII on said bacteriophage. However, the examiner states that Bhardwaj notes the advantages of VIIIp glycoprotein fusions for production and expression of foreign peptide epitope constructions, that Willis further teaches that the genome of bacteriophage fd has been engineered to permit construction of hybrid virus particles in which the wild-type major coat protein gpVIII sub-units were interspersed with coat proteins displaying one or other of two foreign peptides in the exposed N-terminal segments. The examiner states that Willis teaches that the specificity of the immune response, the ability to recruit helper T-cells and the lack of need for external adjuvants suggests that it would also be an inexpensive and simple route to the production of effective vaccines. With respect to claim 5, relating to achieving a titer of antibodies above 1:50,000, the examiner states that Schenk notes titers are produced such that the titers are directed to about 1:87,000. It was not seen that the examiner explained the inclusion of Solomon in this rejection. This rejection is respectfully traversed.

As discussed above, Schenk does not disclose administration of an Aβ epitope displayed on the coat of a bacteriophage. None of the secondary references supply this

deficiency with respect to claim 1. As claim 1 is unobvious, all of the dependent claims must also be unobvious.

Devlin does not supply any of the deficiencies discussed above for claim 1 as Devlin does not suggest that bacteriophage bearing foreign proteins may be used as a vaccine for any purpose. Bhardwaj merely discloses the development of monoclonal antibodies against the gIIIp and gVIIIp of bacteriophage. These monoclonal antibodies can be used in affinity capture phage ELISA. There is nothing in Bhardwaj which would suggest the therapeutic use of bacteriophage displaying a foreign peptide for any purpose.

Willis discloses the immunological properties of foreign peptides in multiple display on a filamentous bacteriophage. Such bacteriophage is used to raise antibodies in mice and rabbits. It suggests, but does not test, that such bacteriophage might be an effective means of vaccine production that will merit further investigation. There is no disclosure with respect to Aβ protein nor is there any disclosure about delivering of any foreign protein to the brain. Further, there is no suggestion that the titer of antibodies will be longer lasting when using bacteriophage than otherwise.

The examiner's attention is invited to the discussion of the Schenk patent at pages 5-8 of the present

specification. Note particularly paragraph [0016], particularly with respect to amount of serum titers and the degree to which these serum titers will persist over time. It has been disclosed in the present specification, see, for example, Figure 21 and Example 9, that injection of phage-carrying epitope elicits a long lasting serum titer of antibodies. This unexpected property is not suggested by Willis.

Furthermore, the ability of phage administered intranasally to bypass the blood-brain barrier is not suggested by any of the references of record. See Example 7, beginning at page 86 of the present specification. The fact that Schenk mentions intranasal delivery among every other possible type of delivery does not suggest the results obtained by the present invention when using intranasal delivery of filamentous phage, nor is this disclosed by Willis. Accordingly, claim 12, requiring administration to the olfactory system of the subject, is particularly free of this rejection.

For all of these reasons, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 1-4, 6-8 and 10 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Frenkel in view of Bhardwaj and as evidenced by Winter. The examiner states that

Frenkel teaches anti-aggregating antibodies that bind to an epitope located as a continuous sequence at the beginning of the N-terminal of βAP and contemplates use of the peptide to control aggregation of βAP *in vivo*. The examiner states that the reference teaches epitope libraries in which different peptides are expressed on the surface of a filamentous phage, including the peptide EFRH, which inhibits binding of monoclonal antibodies to β-amyloid peptide. The examiner states that the reference teaches that the bacteriophage propagates in bacterial flora and in *E. coli*. However, the examiner recognizes that Frenkel does not teach the use of the antigen displayed on the surface of a bacteriophage, nor does it teach the epitope being displayed by a coat protein VIII. The examiner states that Bhardwaj teaches fd and M13 in production of antibodies that react with the gIIIp and gVIIIp coat proteins of phage M13 and also teaches constructs using these peptides for expression of foreign proteins in phage display and the advantages of such constructs in evaluating expression via monoclonal antibodies to the fused protein. The examiner states that Winters discloses selecting human antibodies of desired specificity. The examiner states that it would have been obvious from Bhardwaj for Frenkel to use fd or M13 bacteriophage and to express the β-amyloid epitopes for the purpose of presenting the antigen to the immune system

within the host for production of antibodies. The examiner considers that Frenkel specifically motivates the artisan to substitute the Aβ peptide as the foreign peptide for the purpose of stimulating antibody production for detection and development of compounds to control aggregation of βAP *in vivo*, specifically for eliciting antibodies that inhibit aggregation and/or cause disaggregation. This rejection is respectfully traversed.

As the examiner recognizes, Frenkel does not disclose administration of bacteriophage displaying the epitopes discussed therein, including EFRH. The bacteriophage libraries are only used as tools to find the epitopes recognized by monoclonal antibodies 6C6 and 10D5. There is certainly no suggestion that these tools may be used as a therapeutic. Bhardwaj also is silent about using any filamentous phage as a therapeutic vaccine. Indeed, filamentous phage bearing a foreign protein is not used as an immunogen. If anything, Bhardwaj would make it obvious to use gVIIIp bacteriophage in the library tool used by Frenkel. However, no combination of the two references would provide any motivation to actually administer bacteriophage bearing the desired Aβ epitope for use as a therapeutic vaccine.

Winters discloses the display of human antibody fragments on bacteriophage. It certainly discloses nothing

about administering bacteriophage containing any foreign protein for use as a therapeutic vaccine.

Accordingly, no combination of Frenkel, Bhardwaj or Winters teach or make obvious any of the present claims. Reconsideration and withdrawal of this rejection are also respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. §112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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